

Arbeit unter der Leitung von Prof. Hottinger

Cortisone and Meticorten in the treatment of Infectious Hepatitis in children



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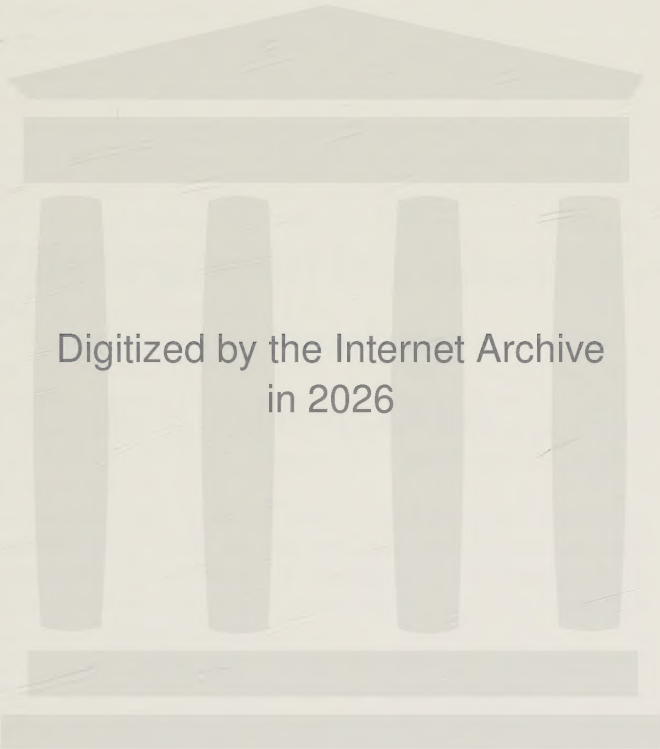
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Von Ralph Katz

Standard therapy of infectious hepatitis has advanced very little in recent decades, and a means of combating the infectious disease itself has not yet been found. Treatment has usually consisted of rest in bed, a low fat, high-carbohydrate, high-protein diet, and the administration of lipotropic substances, vitamins, and parenteral fluids. In cases which do not respond to therapy or in which treatment is impossible because of severe vomiting and anorexia, improvement with cortisone is often dramatic. Anorexia and malaise disappear and a voracious appetite sets in. Serum bilirubin usually decreases rapidly and in many cases the total duration of illness is reduced by as much as two weeks.

The mechanisms by which cortisone exerts its actions in hepatitis are not definitely known. Increase in appetite, permitting maintenance of an adequate caloric intake, is certainly a significant factor, and, together with the glycconeogenic action of cortisone, causes increased storage of glycogen in the liver.

Thorn et al. (42) have shown in animals that cortisone causes an increased flow of bile and this mechanism, as well as the reduction of cholestasis resulting from absorption of inflammatory edema in the liver parenchyma, could account for the rapid fall in serum bilirubin.

Other factors have also been postulated, including an antiallergic effect of cortisone and a direct inhibiting action on the virus of hepatitis, but these are still largely a matter of conjecture. Whether the inhibition of fibrous tissue proliferation by cortisone will reduce the incidence of post-hepatitic cirrhosis has not yet been determined and will require follow-up studies over a period of years.

Because cortisone often increases the tendency of hepatitis patients towards water retention, meticorten would now

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appear to be preferable. It permits the use of a high-protein diet, which necessarily contains a certain amount of salt, and the administration of parenteral fluids. Side effects appear to be similar to those of cortisone, except perhaps for some increase in glycosuria with meticorten (25) (30).

LITERATURE:

The use of adrenal cortical extracts in the treatment of hepatitis was proposed as early as 1937 by Eppinger (12). Before cortisone was generally available, several reports appeared in the literature on the use of adrenal extracts and desoxycorticosterone, but with very variable results (38) (2) (1) (23) (28).

In 1951 Wildhirt (45), in Germany, using adrenal cortical extracts, and in 1952, Ducci and Katz (11) in South America, using ACTH, cortisone, and aureomycin, reported the recovery of several comatose patients. Since then, further recoveries have been reported (32) (15) (8) (20).

Controlled studies on the effects of cortisone or ACTH in hepatitis have been carried out on large series of patients by several teams (13-16) (19) (21) (22) (26) (33-35) (37). Infectious hepatitis, however, is usually a self-limited disease with a very low mortality rate, which often shows considerable variation in its clinical manifestations and in its severity from one epidemic and from one patient to another. Consequently, although a great deal of work has been done on the subject, results have frequently been contradictory and there is still considerable difference of opinion concerning the value of cortisone therapy.

There is, however, general agreement among these authors that rapid improvement in appetite and subjective well-being occurred in most of their patients with cortisone or ACTH treatment. Huber and Wiley (21) found that although all patients were urged to eat as much as possible, food uptake was 20% higher in 100 cortisone treated patients than in a comparable control group.

Evans et al. (13) (14) found that bilirubin was significantly reduced in patients receiving cortisone or ACTH and that normal levels were reached as much as two weeks earlier than in control patients. The results obtained by Heilmeyer et al. (20) were very similar, normal values being reached by the cortisone group 23 days before the control group. Other

observers, however, found that cortisone caused a slight early fall in serum bilirubin, but that control groups reached levels similar to those of cortisone groups approximately two weeks after institution of therapy (21) (37).

The tests of liver function have frequently given contradictory results in the various studies. It appears, however, that the tests of excretory function, the bromsulfalein and alkaline phosphatase, are normalized more rapidly with cortisone (14) (21), while tests depending on serum proteins are affected less. Huber and Wiley (21) report that the cephaline flocculation returned to normal somewhat more rapidly with cortisone, but this was not confirmed in other studies (20)(37).

The total duration of illness has usually been found to be reduced by cortisone therapy. Various authors have reported that recovery occurred 14 days (14) (20), and 5 days (21) earlier with cortisone than in patients not receiving cortisone. In one study (37) the duration of illness was not changed, perhaps because a relatively large number of cortisone treated patients relapsed when treatment was stopped.

Relapses constitute one of the most serious complications of hormone treatment, especially because they are rarely encountered when cortisone or ACTH is not used (14) (37). They usually occur when cortisone is stopped or while the dosage is being reduced and tend to be more severe than the original disease. The incidence of relapses has been reported as 25% (37), 20% (14), 4% (20), and 0 (21) by various authors. Gamma globulins were found to be reduced in patients treated with cortisone (14), and it is believed that relapses may be the result of interference with antibody production (14) (16). It is interesting in this respect, that relapses under ACTH therapy were seen by Evans et al. (14) only in those patients who received ACTH within 10 days after onset of symptoms, and not in those started on treatment later in the course of the disease. The attempt to reduce relapses under cortisone treatment by the simultaneous administration of gamma globulins, however, was not successful (16). Huber and Wiley (21) saw no relapses in 100 patients treated with cortisone, a fact which the authors attribute to the gradual lowering of the dosage during the course of treatment and the administration of small doses of cortisone before it was stopped completely. This was also done in other studies, however, in which 25% (37) and 20% (14) of the patients relapsed. It may therefore be

significant that in Huber and Wiley's study (21), the average duration of illness before institution of treatment was 13 days, although one cannot draw conclusions concerning relapses with cortisone from a study of ACTH therapy (Evans et al.). With ACTH, relapses appear to be at least as frequent as with cortisone (7) (13) (24) (32), especially when treatment is not continued for at least several weeks or until the disease is no longer active (18) (24) (33). This probably has to do with the exhaustion of the adrenal cortex by additional stimulation during a period of stress. However, it is possible that relapses may be prevented by short term administration of ACTH after completion of cortisone treatment, as suggested by Heilmeyer (19).

Of the known side effects of cortisone, fluid retention and glycosuria have been observed quite frequently. Severe weight gain and edema were seen primarily when large doses of cortisone were used. Koller et al. (26), using 200 mg of hydrocortisone per day, report an average weight gain of 9 kg in 50% of their patients in spite of salt restriction and the administration of potassium chloride. This gain in weight was much greater than in patients treated with equal doses of cortisone for diseases other than hepatitis, and occurred despite the fact that serum proteins increased in some patients during this time. Fluid retention was infrequent in studies employing smaller doses of cortisone (14) (21) (37), and Huber and Wiley (21) state that edema occurred when 100 mg of cortisone per day were given but disappeared when the dosage was reduced to 50 mg. Koller et. al. (25) found that when meticorten was used no increase in weight occurred, and that patients even lost weight which they regained after therapy was terminated.

Glycosuria was observed frequently but was usually transitory and disappeared during the course of treatment (14) or when cortisone was stopped (21). Occasionally, however, treatment did have to be interrupted because of severe hyperglycemia (21). Psychic disturbances also occurred several times, necessitating interruption of therapy (21). Hypertension has been an infrequent complication. Fulminant infections, which have occasionally been reported (26) might be reduced by the prophylactic administration of an antibiotic.

Because of the frequency and severity of the complications in cortisone treatment, most authors are of the opinion that it

should be reserved for severe cases and for those which do not respond to conventional treatment. ACTH appears to be inferior to cortisone (13) (14) and some authors consider it ineffective in the treatment of hepatitis (22).

Concerning chronic hepatitis, cortisone (41) and ACTH (17) (18) (33) were tried and found to be of at least temporary benefit, but here fluid retention became impossible to control and frequently lead to ascites or bleeding from esophageal varices (18) (33). In the treatment of comatose patients, most authors agree that the prognosis is so poor with conservative therapy that cortisone may be given a trial. However, Koller et al. (26) warn that extreme caution should be used, Heilmeyer et al. (20) do not consider it effective in comatose patients, and Wildhirt (46), attributing fatty degeneration of the liver directly to the use of cortisone, goes so far as to say that it has no place in the treatment of hepatitis.

It is interesting to note that although a great deal of work has appeared in the literature on the use of cortisone in viral hepatitis with adults, no reference to its use in children can be found. This may be because the disease is usually milder and of shorter duration in children than in adults (3) (4) (6) (10) (39), and is frequently anicteric (4) (10), sometimes even in fatal cases (29) (39). It is a general rule that the younger the patient the milder the disease (39). In children over the age of ten, the disease is more severe, usually with jaundice, and similar to the form seen in adults (31). Nevertheless, fatal cases have been reported quite frequently in children of all ages with massive liver cell necrosis (29) (40) (43) (44) or from posthepatic cirrhosis (9) (40) (27).

In our own area, infectious hepatitis has been extremely benign, and although the disease has become more frequent, no fatal cases have been seen for over 15 years. During this time, one or two cases may have gone over into the chronic form, which appears to occur independently of the severity of the acute disease. Encouraged by the favorable results obtained with adult patients, we have treated several children with cortisone or meticorten. Because more severe cases with a high serum bilirubin were selected for treatment, the group consists only of older children.

Case 1 - E.R.:

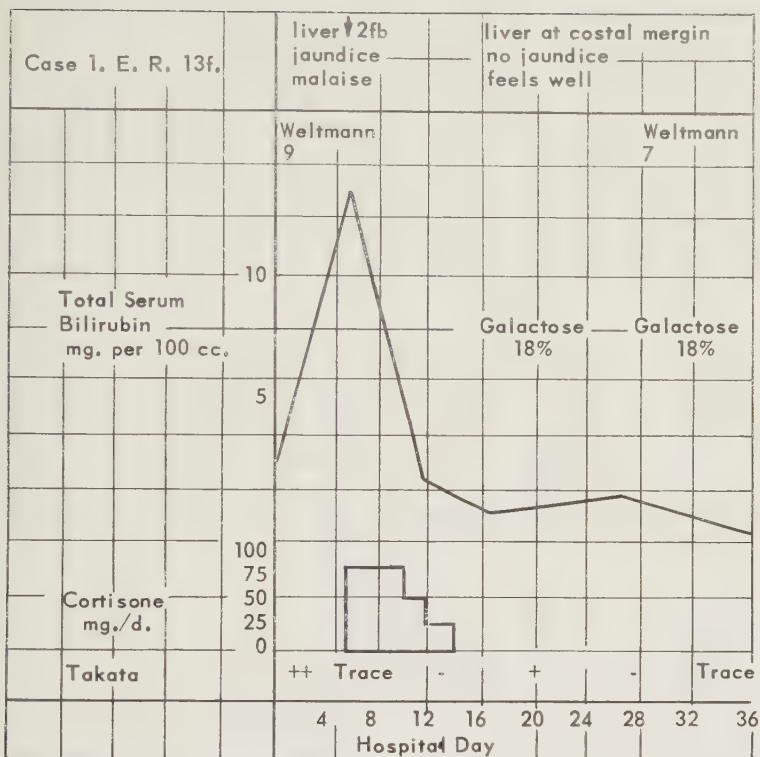
This 13 year old girl was admitted to the Children's Hospital in Basel with a history of low grade fever, malaise, anorexia, and

abdominal distress of four days' duration. Two days prior to admission, a yellow discoloration of the scleras had been noted.

Physical examination revealed a 13 year old girl, slightly jaundiced but in no distress. The liver was palpable two fingerbreadths below the costal margin and was not tender. The spleen was not palpable. Temperature and pulse were normal. Laboratory Data: Blood studies showed 4,500,000 erythrocytes, 14.5 gm. of hemoglobin, and 6,500 white cells with a normal differential count. Urine examinations showed a trace of albumin and no sugar, cells, or casts. The test for bilirubin was strongly positive and urobilinogen was present in normal concentration. Total serum bilirubin was 3.5 mg. in 100 cc.. The Takata was strongly positive. The erythrocyte sedimentation rate was 6/15/90. The Weltmann Coagulation test was 9.

Therapy consisted of bed-rest, diet, warm compresses, and the administration of vitamins and a mixture of amino acids. During the first few days, the child remained afebrile and ate well, but jaundice deepened steadily. Five days after admission, the Takata test was only slightly positive but serum bilirubin had risen to 13.8 mg. per 100 cc.. At this time, cortisone therapy was instituted, 100 mg. per day for three days, then 75, 50, and 25 mg. per day, each for two days. Within five days, serum bilirubin had dropped to 2.3 mg. per 100 cc.. The child felt well and her appetite had increased. The urine was negative for bile, and the Takata had become negative. Cortisone was stopped on the 14th hospital day and the child continued to feel well. Serum bilirubin was 1.2 mg.% and the Takata again negative. The following week, bilirubin was again 1.8 mg.%, the Takata negative, the liver was at the costal margin and not tender, but the galactose excretion continued to be too high, and the Weltmann Coagulation test was 7. The child was discharged after having spent 38 days in the hospital but returned to the out-patient department two weeks later at which time all laboratory studies were normal.

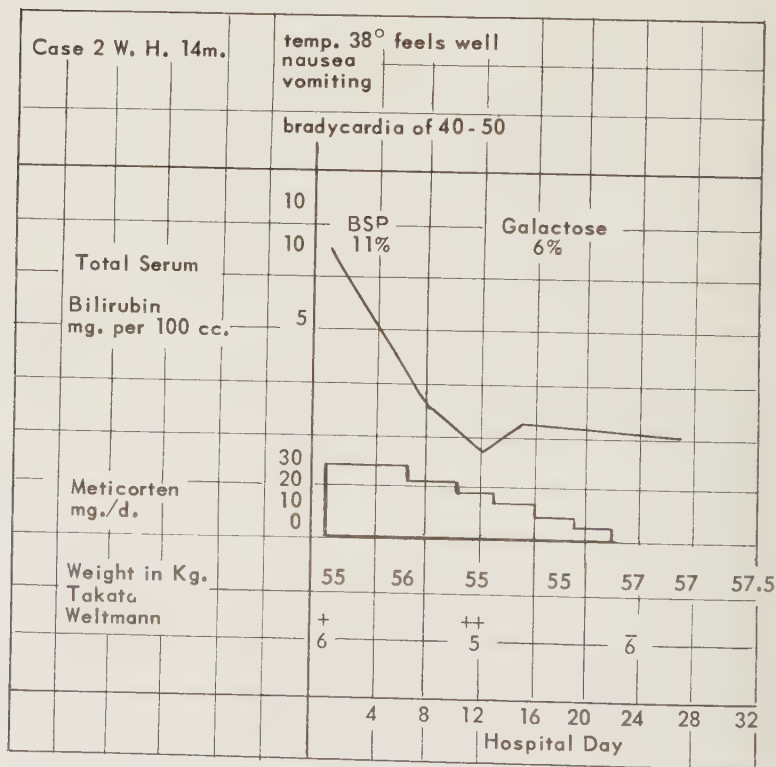
Comment: This 13 year old child, suffering from infectious hepatitis, showed progressive deepening of jaundice and reached a serum bilirubin level of over 13 mg.%, the highest we have seen in a child in recent years, prior to institution of cortisone therapy. Within a few days, bilirubin had dropped to 2.3 mg.% and cortisone was stopped after only nine days, apparently without ill effects, although bilirubin increased slightly, from 1.2 to 1.8 mg.%. No side effects of cortisone were noted and body weight remained stationary throughout.



Case 2 - W.H.:

A fourteen year old boy, W.H., was admitted with a history of anorexia, vomiting, abdominal distress, and tiredness for the past eight days. Two days prior to admission, he had become jaundiced and had had a temperature of 38.5°C . On admission, the boy complained of nausea. The patient was seen to be a well developed, well nourished boy of 14. He was jaundiced and had a temperature of 37.8°C . Physical examination was otherwise negative. Laboratory studies showed a normal red cell count, hemoglobin, and leucocyte count. The urine was negative for albumin, sugar, cells, and casts, but was strongly positive for bilirubin. Total serum bilirubin was 8 mg. per 100 cc., the Takata test positive, and the Weltmann coagulation band 6. The patient was placed on a diet and was given vitamins and amino acids, but he continued to complain of severe nausea. On the sixth hospital day, meticorten and aureomycin were begun. Meticorten was given in a starting dose of 30 mg. per day for six days, then slowly reduced every three days by 5 mg., making a total dose of 405 mg. over a period of 21 days. The day after meticorten was started, serum bilirubin was 3.8 mg.%, on the third day after meticorten it was 2.2 mg.%, and on the fifth day 0.7 mg.%.

Nausea and malaise disappeared shortly after meticorten was started but bradycardia, which had set in during the first days continued for approximately three weeks. An electrocardiogram was done and was normal. After six days, when the dosage of meticorten was decreased by 5 mg., serum bilirubin increased slightly to 1.5 mg.% where it remained for 14 days and then decreased to 1 mg.%. Galactose tolerance and bromsulfalein were both normal, 6% and 10% respectively. During the time when larger doses of meticorten were being given, body weight remained stationary but after meticorten was reduced to 5 mg. per day, weight increased from 55 to 57.5 kg.. The patient was discharged 35 days after he entered the hospital.



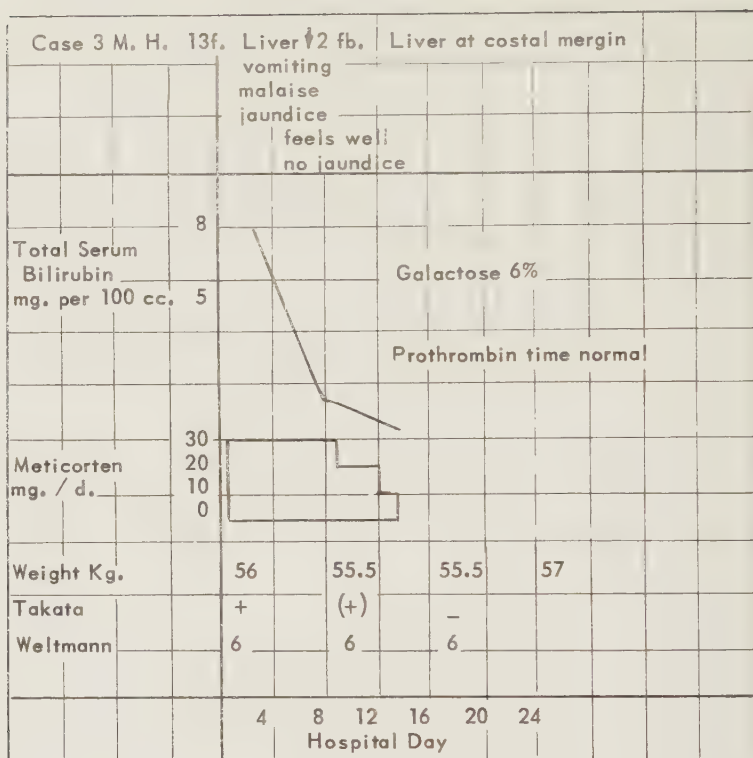
Comment: It is impossible to know in this case whether decrease in serum bilirubin was accelerated by the use of meticorten. Certainly the improvement in the subjective state of the patient was impressive. The fact that weight gain did not occur until after meticorten was stopped is in agreement with

the findings of Koller et al. (25) who believe that meticcorten may have a diuretic action and observed weight loss during the course of treatment and increase in weight afterwards.

Case 3 - M.H.:

This 13 year old girl was the sister of the patient described above and entered the hospital four weeks after her brother. She gave a history of four days of anorexia, abdominal pain, and vomiting. The urine during this time was dark and the stools light. On the day before she was admitted to the hospital, a yellow color of the scleras had been noted and on the day of admission, jaundice of the skin had appeared. Physical examination revealed a well developed, well nourished girl of 13. The skin was icteric and the turgor good. Heart and lungs were normal. The liver was palpated two fingerbreadths below the costal margin. The spleen could not be palpated. There was slight right upper quadrant tenderness. Laboratory studies showed 4,700,000 erythrocytes, 16 grams of hemoglobin per 100 cc., and 4,700 white blood cells. Urinalysis revealed a trace of albumin, no sugar, cells, or casts, normal urobilinogen and a positive test for bilirubin. The erythrocyte sedimentation rate was 14/28/71. Serum bilirubin was 8 mg. in 100 cc., the Takata was positive, and the Weltmann was 6.

Starting on the second hospital day, the girl was given meticcorten, 30 mg. per day for eight days, then 20 and 10 mg. per day, each for three days. In addition she received 250 mg. per day of aureomycin, and the standard hepatitis diet and vitamins. Symptomatic improvement occurred almost immediately and the girl felt well. By the fifth day, jaundice had disappeared, the urine was negative for bilirubin, and the liver was one fingerbreadth below the costal margin. On the tenth hospital day serum bilirubin was 2 mg.%, the Takata slightly positive, the Weltmann 6, and the liver was at the costal border. On the fifteenth day serum bilirubin was 0.7 mg.%, the Takata negative, and the erythrocyte sedimentation rate 7/16/80. Because epistaxis had occurred several times, the prothrombin time and the bleeding and coagulation time were determined, all of which were within normal limits. A galactose test performed at this time was also normal, 6% of the total amount being excreted. The child showed little change in body weight, having weighed 56 kg. prior to meticcorten therapy, 55.5 kg. during the time meticcorten was given, and 57 kg. after treatment was stopped. She was discharged on the 25th hospital day.

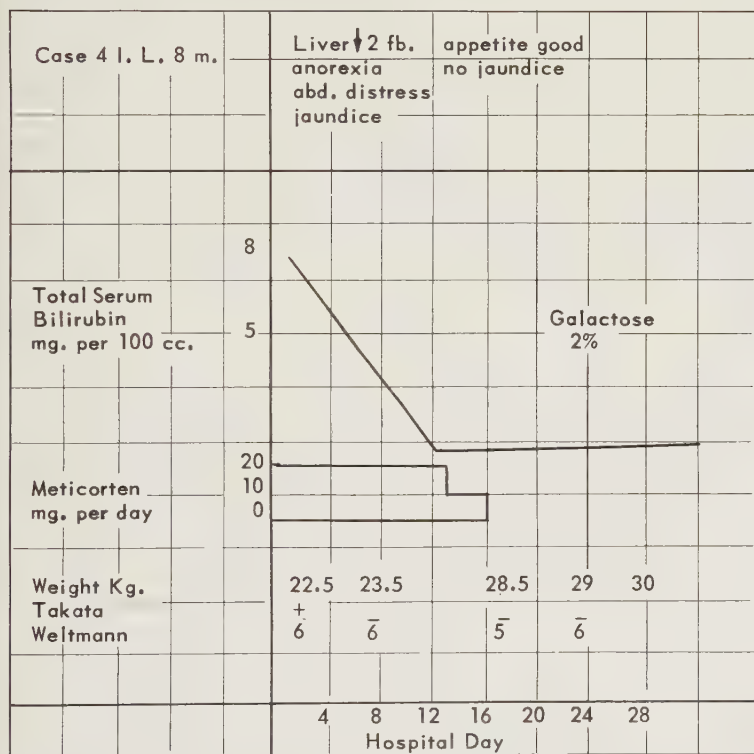


Case 4 - J.L.:

This 8 year old boy had had malaise for approximately two weeks prior to admission and it was thought that he had influenza. Four days before admission he had started to vomit severely and was unable to eat, but complained of severe thirst. On the day of admission he became jaundiced. Physical examination revealed a well developed, jaundiced boy of 8, who appeared to be poorly nourished. His weight was 22.5 kg., 7 kg. below the normal weight for his age and size. Physical examination was otherwise negative except that the liver extended one finger breadth below the costal margin. Blood studies showed 4,200,000 red blood cells, 15.2 grams of hemoglobin, and 8,000 white cells with a normal differential count. The urine was negative for albumin, sugar, cells, and casts. Urobilinogen was increased and bilirubin was positive. Serum bilirubin was 8 mg. per 100 cc., the Takata was positive, the Weltmann 6 tubes, and the sedimentation rate 11/26/84.

Meticorten therapy was begun immediately in doses of 20 mg. per day for nine days and then 10 mg. per day for three days, together with aureomycin. Appetite and well being set in immediately

and jaundice disappeared. Seven days later serum bilirubin had decreased to 0.5 mg.% and the Takata had become negative. The liver was at the costal margin. After meticorten therapy was stopped the Takata remained negative and serum bilirubin changed only insignificantly to 0.6 and 0.9 mg.%. During the hospital course, the child's weight increased from 22.5 to 23.5 kg. during the first week, to 28.5 kg. in the second week, and to 29 and 30 kg. in the third and fourth weeks and some rounding of the face was noted. The boy was discharged on the 30th hospital day.

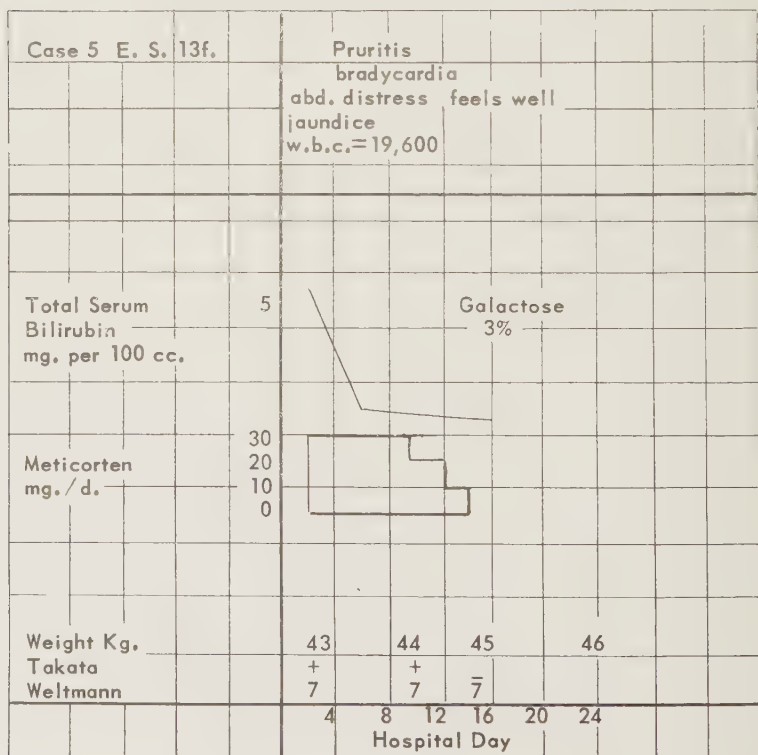


Comment: It is difficult to evaluate the effect of meticorten on the increase of body weight in this case. On admission, although the child was 7.5 kg. under the normal weight for his age and height, he did not appear dehydrated despite several days of severe emesis. Hemoconcentration was not present. The weight gain of 7.5 kg., and especially the gain of 5 kg. during the second week with rounding of the face, show fluid retention under meticorten therapy.

Case 5 - E.S.:

This 13 year old girl was admitted with a history of five days of anorexia and abdominal distress and one day of jaundice. She complained of generalized pruritus. The liver was palpable one finger-breadth below the costal margin and the spleen was not felt. The pulse was 92 per minute. Laboratory studies: Blood examination showed a leucocytosis of 19,600 with a shift to the left, 4,400,000 red blood cells, and 15.2 grams of hemoglobin. The erythrocyte sedimentation rate was 14/31/77. Bilirubin in the serum was 5.2 mg.%, and the Takata was positive. Urinalysis showed a trace of albumin, no sugar, cells, or casts. The urine gave a positive reaction for bilirubin.

Meticorten and aureomycin therapy was instituted on the third day, together with diet and vitamins. Meticorten was given in doses of 30 mg. per day for nine days followed by 20 and 10 mg. per day, each for two days. On the fourth day, bradycardia between 50 and 55 per minute set in and continued until the fourteenth day. Pruritus over the entire body became more severe and also continued until the fourteenth day. On the ninth hospital day, the Takata was still



positive but bilirubin was no longer present in the urine and serum bilirubin was 1.3 mg.%. After the sixteenth day, when meticorten had been discontinued, the Takata had become negative, serum bilirubin was 0.3 mg.%, and the sedimentation rate was 6/12/72. The girl now felt well. The liver was still enlarged to two fingerbreadths below the costal margin. A galactose tolerance test was normal. The child's weight had increased slowly from 43 to 46 kg. during her time in the hospital. She was discharged after a hospital course of 26 days.

Comment: We are not certain that meticorten had a beneficial effect in this case. Serum bilirubin was not very high on admission and the symptoms were perhaps too mild to permit evaluation of therapy. Serum bilirubin did decrease within a week from 5.2 to 1.3 mg.% but, in contrast to adults, this drop is not much faster than what one often sees in children not treated with adrenal steroids. In addition the Takata remained positive and bradycardia and severe pruritus were present for the entire time that meticorten was being given.

GENERAL COMMENT

Although a group of five cases certainly does not permit statistical conclusions to be drawn, we have the impression that improvement in the subjective state of the patients and a more rapid return to normal levels of serum bilirubin occurred in most of these children with cortisone or meticorten therapy. We did not observe any severe complications attributable to medication.

SUMMARY

The literature on the treatment of viral hepatitis with cortisone is reviewed and the mechanisms by which cortisone may exert its effects are discussed. It is noted that no literature exists specifically on the treatment of hepatitis in children with cortisone.

Five children with infectious hepatitis were treated with cortisone or meticorten. Symptomatic improvement promptly occurred in at least four of the five cases, and serum bilirubin returned to normal more rapidly than could have been expected without adrenal hormone treatment. No side effects of therapy were observed.

ZUSAMMENFASSUNG

Die Literatur über die Behandlung der virus hepatitis mit Cortison und dessen Wirkungsweisen wurden besprochen. Es wird bemerkt dass keine Spezialliteratur existiert über die Cortisonbehandlung der Hepatitis im Kindesalter.

Fünf Kinder mit hepatitis epidemica wurden mit Cortison bzw. Meticorten behandelt. In vier Fällen trat eine sofortige symptomatische Besserung auf und der Bilirubinspiegel wurde rascher normalisiert als ohne die Therapie zu erwarten gewesen wäre. Es wurden keine Nebenwirkungen beobachtet.

RESUMÉ

Dans ce travail on fait un résumé de littérature à propos du traitement des hépatites à virus par la cortisone, et ses modes d'action sont discutés. On remarque qu'il n'existe pas de littérature médicale sur le traitement par la cortisone de l'hépatite chez l'enfant.

Cinq enfants atteints d'hépatite épidémique ont été soignés les uns par la cortisone, les autres par le méticortène. Dans quatre cas on constate une amélioration symptomatique rapide et le taux de bilirubine dans le sang a été normalisé plus rapidement qu'on l'aurait attendu sans thérapie.

On ne remarque aucune réaction secondaire.

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CURRICULUM VITAE

Ich bin am 9. Juni 1931 in Heidelberg, Deutschland, geboren.

In 1939 wanderte meine Familie nach Amerika aus nach Buffalo, New York, wo ich seither wohnhaft bin. Dort besuchte ich bis 1948 die Primar- und Sekundarschule, und studierte dann bis 1951 an der University of Buffalo wo ich den Bachelor of Arts Degree erhielt. Ich began mein medizinisches Studium an der Universität Heidelberg (Deutschland) in 1951 und absolvierte nach drei Semestern die Anatomische Prüfung. Nach zwei klinischen Semestern in Heidelberg setzte ich 1954 mein Studium fort an der Universität Basel und bestand im Herbst 1956 die Fachprüfung für Aerzte.

